Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

By the present amendment, the specification has been amended to recite the phrase that the present application claims priority from PCT/US2003/05032, filed February 19, 2003, which is a continuation-in-part of 10/079,049, filed February 19, 2002, now U.S. Patent No. 6,635,677, which is a continuation-in-part of U.S. 09/373,693, filed August 13, 1999, now U.S. Patent No. 6,465,488.

Claim 59 has been amended to include the language that the base excision repair (BER) inhibitor is selected from the group consisting of an AP endonuclease inhibitor, a DNA glycosylase inhibitor, a DNA polymerase inhibitor, and a DNA ligase inhibitor.

Claim 64 has been amended to eliminate its multiple dependency. Claims 230-233 have been added to the present application. Support for these claims can be found on page 4, lines 29-31, and page 5, line 12 of the present application. Claims 70, 93, 99 and 100 have been cancelled.

Below is a discussion of the 35 U.S.C. §112, first paragraph rejection of claims 64, 67, and 100, the 35 U.S.C. §112, first paragraph rejection of claims 59-60, 64-65, 70, 75, 77, 78, 93, and 98-100, and the 35 U.S.C. §102(b) rejection of claims 59-60, 75, and 98.

1. Lack of written description under 35 U.S.C. §112, First Paragraph, rejection of claims 64, 67 and 100

Claims 64, 67 and 100 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter, which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As discussed above, claim 100 has been cancelled and claim 67 is withdrawn. Therefore, the rejection of claims 100 and 67 under 35 U.S.C. §112 is moot.

With respect to pending claim 64, the Office Action argues that use of the term "AP endonuclease inhibitors" as recited in claim 64 does not suffice to meet the written description requirement under 35 U.S.C. §112, first paragraph.

Applicants respectfully traverse this rejection because: (1) the specification of the application clearly allows persons of ordinary skill in the art to recognize that Applicants were in possession of "AP endonuclease inhibitors" as recited in claim 64; and (2) the Office Action has failed to establish a prima facie case that the specification does not satisfy the written description requirement.

Referring to MPEP 2163.02,

> "The fundamental factual inquiry [for determining compliance with the written description requirement] is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d

> 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)."

The specification of the present application describes AP endonuclease inhibitors by specific examples, formulas, and characteristics such that one skilled in the art would recognize that Applicants had possession of the claimed invention.

Page 18, lines 18+ notes that AP endonuclease inhibitors can include:

> "Methoxyamine (MX), N-ethylmaleimide, O^6-benzylguanine, and compounds having structures of formula I: wherein X is O or NH, Y is O, S, or NH, Z is absent or represents O, S, or NH, and R represents a hydrogen or a hydrocarbon moiety, and pharmaceutically acceptable salts thereof."

Page 19, lines 1+ further notes that:

> "Suitable AP endonuclease inhibitors may act by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds, or by acting directly on AP endonuclease. Other compounds that may possess AP endonuclease inhibitory activity (e.g., by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds) include Other potential inhibitors include O-benzylohydroxylamine; ethyl aminooxyacetate; aminooxyacetic acid; ethyl aminooxyacetate; $H_2NOCHMeCO_2H$; carboxymethoxyamine; aminooxyacetic acid; $HN{=}C(NH_2)SCH_2CH_2ONH_2$; $H_2NO(CH_2)_3SC(NH_2){=}NH$; $MeOC(O)CH(NH_2)CH_2ONH_2$;$H_2NOCH_2CH(NH_2)CO_2H$; canaline; $H_2NO(CH_2)_4ONH_2$; O-(p-nitrobenzyl)hydroxylamine; 2-amino-4-(aminooxymethyl)thiazole; 4-(aminooxymethyl)thiazole; O,O'-(o-phenylenedimethylene)dihydroxylamine; 2,4-dinitrophenoxyamine; O,O'-(m-phenylenedimethylene)dihydroxylamine; O,O'-(p-phenylenedimethylene)dihydroxylamine; $H_2C{=}CHCH_2ONH_2$; $H_2NO(CH_2)_4ONH_2$; $H_3C\text{--}(CH_2)_{15}\text{--}O\text{--}NH_2$, 2,2'-(1,2-ethanediyl)bis(3-

> aminooxy)butenedioic acid dimethyl diethyl ester; compounds having any of the following structures: and pharmaceutically acceptable salts of any of these compounds."

Accordingly, Applicants have clearly provided specific examples of AP endonuclease inhibitors as well as characteristics that can be used to classify such compounds.

The specification also discloses a method of identifying additional AP endonuclease inhibitors for use in the present invention. The specification describes a high throughput screening assay to identify new inhibitors of BER, which have the ability to block AP site cleavage.

Page 37, line 31 to page 39, line 71 (and Fig. 23A and 23B) state:

> "High-throughput screening methods include two molecular reaction assays:
> 1. Analysis of chemical--modified AP Sites assayed by Aldehyde Reactive Probe (ARP). This is a competitive assay to measure the reactivity with AP site between ARP reagent (Dojindo Molecular Technologies Inc., Gaithersburg, Md.) and the screening compounds. ARP and MX have a similar reactivity with AP sites. They react specifically with an aldehyde group that is open ring form of the AP sites. Thus this assay will allow identification of compounds with potential to block AP site repair based on the binding affinity and efficiency to AP sites of screening compounds compared to ARP and MX.
> a. AP site standard preparation: AP sites were produced in a calf thymus DNA by heat/acid-buffer solution. Intact calf thymus DNA was added to sodium citrate buffer (10 mM sodium citrate containing 10 mM $NaH._2PO_4$ and 10 mM NaCl, pH 5.0) and held at 70 °C. for 30 min. The reaction was stopped by chilling rapidly on ice, and the DNA was then precipitated with cold ethanol, washed with 70% ethanol, dried, and resuspended in sterilized distilled water.
> b. AP-DNA (15 pg) was incubated with test compounds at different concentrations at 37 °C. for 30 min prior to ARP (1 mM) or ARP alone (Dojindo Molecular Technologies Inc., Gaithersburg, Md.) for 30 min. After precipitation and wash with ethanol, DNA was resuspended in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.2). DNA was heat-denatured at 100.degree. C. for 5 min, quickly chilled on ice, and mixed with an equal amount of 2 M ammonium acetate. The single-stranded

> DNA was then immobilized on a BAS-85 NC membrane (Schleicher and Schuell) using a vacuum filter device (Schleicher and Schuell). The NC membrane was incubated with streptavidinconjugated horseradish peroxidase (BioGenix) at room temperature for 30 min. After NC membrane was rinsed with washing buffer containing NaCl (0.26 M), EDTA (1 mM), Tris-HCl (20 mM), and Tween 20 (1%), ARP-AP sites are visualized with ECL reagents (Amersham Corp.) (FIG. 22A) and quantitated by scanning densitometer (FIG. 22B).
> 2. AP sites cleavaged by AP-endonuclease (APE). This assay confirms that AP sites modified by potential BER inhibitors are resistant to cleavage by APE, (Trevigen, Gaithersburg, Md.) a BER protein. The assay may be performed as follows (see also FIGS. 23A and B):
> a. AP site is prepared by replacing single nucleoside with deoxyuridine in duplex oligonucleotides (40 mer).
> b. Regular AP site is produced in the duplex oligonucleotides by human uracil DNA glycosylase (LIDGase, Trevigen, Gaithersburg, Md.) to remove the uracil residue.
> c. To generate MX-adducted AP site substrates: the UDG-treated duplex oligonucleotides are mixed with 10 mM MX in buffer containing 10 mM KPO4, pH 7.1 and incubated at 37 °C. After 30 min, the substrates are recovered by ethanol precipitation, lyophilized, resuspended in water, and stored at -20 °C.
> d. APE-cleavage reaction: DNA substrates containing either regular AP-sites or chemicalmodified AP sites are incubated with APE (Trevigen, Gaithersburg, Md.) for 30 min and reactants are precipitated with 100% cold ethanol, washed with 70% ethanol and resuspended in TE buffer. The reactants are resolved by denaturing 20% polyacrylamide gel electrophoresis and visualized by silver staining (Silver Staining Kit, Pharmacia Biotech)."

Thus, not only does the specification disclose specific AP endonuclease inhibitors and an assay to identify new AP endonuclease inhibitors of BER, the specification identifies a specific functional characteristic of potential BER inhibitors (blocking AP site cleavage).

The Federal Circuit has stated that the written description requirement does not require the applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he

or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989) (citations omitted).

As discussed above, the specification clearly allows one skilled in the art to recognize what is claimed based on the disclosure of the characteristics of AP endonuclease inhibitors, the disclosure of a vast number of AP endonuclease inhibitors, as well as means to identify additional AP endonuclease inhibitors. Therefore, in view of the foregoing, Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, they were in possession of the invention, and the invention, in that context, is claimed.

Additionally, regardless of the sufficiency of the disclosure in the specification, the Office Action has failed to establish a prima facie case that the specification does not satisfy the written description requirement. The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

The Office Action has failed to provide any evidence in fact or reasoning that the specification fails to meet the written description requirement. The Office Action has merely cited various Federal Circuit decisions without correlating the decisions with the specific disclosure in the present application.

The Office Action argues that enablement of the term "AP endonuclease inhibitors" is analogous to enablement of a genus under 35 U.S.C. §112, first paragraph citing *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). In *Eli Lilly*, the court determined that a description of a genus of cDNA's may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. The court also held that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself, not merely a recitation of its function or a reference to a potential method for isolating it. (*119 F.3d at 1566-1567)*.

Eli Lilly is inapposite to the present application because the claim term at issue is not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. Instead, the claims refer to AP endonuclease inhibitors, which are useful in the methods of the present invention. In contrast to the term "cDNA", that clearly does not describe the actual sequence of the cDNA, the term "AP endonuclease inhibitors" convey exactly what they are. This difference alone sufficiently distinguishes *Eli Lilly*, because when used, as here, merely to identify types of BER inhibitors (instead of undescribed previously unknown DNA

sequences, the use of the well known term "AP endonuclease inhibitors" readily conveys distinguishing information concerning their identity such that one of ordinary skill in the relevant art could "visualize or recognize the identity of the members of the genus." *Eli Lilly, 119 F.3d at 1567,1568*.

The Office Action also cites *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1886, 1892 (CAFC 2004) stating:

> "A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function…"

In *Rochester,* a disputed patent claimed all compounds that could inhibit the cox-2 enzyme without inhibiting the cox-1 enzyme. According to the Rochester court, it was inappropriate for the patentee to make this claim when it had not identified these compounds structurally but, rather, had only suggested an assay that might be used to identify the compounds. In the present application, Applicants have provided more than to just suggest an assay, which might be used to identify useful compounds.

As discussed above, the present application describes specific AP endonuclease inhibitors for use in the present invention (e.g., methoxyamine), the general structure (e.g., Formula 1) of compounds useful as AP endonuclease inhibitors in the present invention, a specific functional characteristic of potential BER inhibitors (blocking AP site cleavage), and an assay to identify new BER inhibitors. Since the specification adequately discloses a combination of identifying

characteristics that distinguish the claimed invention from other materials, it would lead one of skill in the art to the conclusion that Applicants were in possession of the claimed species.

Moreover, the Office Action has provided no evidence to doubt veracity of the statements made in the specification or to show in any manner that the subject matter recited in the application and claims is unpredictable. It is well established that a general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description. MPEP 2163.04. Accordingly, Applicants respectfully request that the 112 first paragraph written description rejection of claim 64 be withdrawn because the specification of the application clearly allows persons of ordinary skill in the art to recognize Applicants were in possession of "AP endonuclease inhibitors" as recited in claim 64, and the Office Action has failed to established a prima facie case that the specification does not satisfy the written description requirement.

2. Claim Rejection - 35 U.S.C. § 112 - Scope of Enablement, rejection of claims 59, 60, 64, 65, 70, 75, 77, 78, 93, and 98-100

Claims 59, 60, 64, 65, 70, 75, 77, 78, 93, and 98-100 are rejected under 35 U.S.C. 112, first paragraph, for failure to comply with the enablement requirement.

The Office Action argues that to practice the present invention as claimed in the current application, a person of ordinary skill in the art would have to engage in undue experimentation. The Office Action specifically argues that the specification does not reasonably provide enablement for treating the broader method of potentiating a therapeutic effect of anticancer agents, which induce formation of AP sites.

Applicants traverse the foregoing rejection as applied to the currently amended claims and submit that the amount of direction or guidance disclosed in the specification is sufficient to enable the skilled artisan to make and use the claimed methods using only routine experimentation.

Applicants have disclosed in the instant specification known anticancer agents and the use of such agents to induce formation of AP sites as recited in claim 59. Specifically, the specification recites at page 22, lines 19+, that:

> "Anticancer agents that induce the formation of AP sites include intercalating agents such as bleomycin, adriamycin, quinacrine, echinomycin (a quinoxaline antibiotic), and anthrapyrazoles.
>
> Radiation, such as gamma radiation, UVA, and UVB, can be used to generate AP sites according to the methods of the invention. Ultraviolet light is absorbed in DNA with the formation of UV-specific di-pyrimidine photoproducts. Exposure to gamma irradiation, UVA, and UVB can induce damaged pyrimidine photodimers.
>
> Anticancer agents that induce the formation of AP sites include DNA oxidizing agents such as hydrogen peroxide.
>
> Anticancer agents that induce the formation of AP sites include alkylating agents such as temozolomide (TMZ), 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), $MeOSO_2(CH_2)_2$-lexitropsin (Me-Lex), cis-diamminedichloroplatinum II (cisplat; cis-DDP), mitomycin bioreductive alkylating agents, quinones, streptozotocin, cyclophosphamide, nitrogen mustard family members such as chloroambucil, pentostatin (and related purine analogs), fludarabine, bendamustine hydrochloride, chloroethylating nitrosoureas (e.g., lomustine, fotemustine, cystemustine), dacarbazine (DTIC), and procarbazine. In certain embodiments, the alkylating agent is a nitrosoruea such as a mustine, i.e., a compound having a structure of Formula II, wherein R is an optionally substituted hydrocarbon substituent, such as an alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, aralkyl, or a heteroaralkyl: In preferred embodiments, R is a substituent shown below or to the right of Formula I, i.e., the chemotherapeutic is carmustine (BCNU), chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, or semustine. In certain related embodiments, the chloroethyl group of Formula I is replaced by a

> methyl group, as in streptozocin. In certain embodiments, however, R is not 2-chloroethyl, i.e., the compound is not BCNU.
>
> Alkylating agents can function by adding methyl groups to DNA, cross-linking macromolecules essential for cell division, and linking guanine bases in DNA through their N^7 atoms. Both inter- and intra-strand cross-links can be mediated by alkylating agents. Inter-strand cross-links prevent the separation of the DNA strands necessary for cell division, and by being more difficult to repair, constitute the more lethal lesion.
>
> In certain embodiments, the anticancer agent is selected from radiosensitizers such as 5-iodo-2'-deoxyuridine (IUdR), 5-fluorouracil (5-FU), 6-thioguanine, hypoxanthine, uracil, ecteinascidin-743, and camptothecin and analogs thereof.
>
> In certain embodiments, the anticancer agent is not temozolomide. In certain embodiments, the anticancer agent is not BCNU. In certain embodiments, the anticancer agent is not PE128723, 6-AN, 3-AB, BCNU, or temozolomide."

These known anticancer agents can be used to treat various cancers. The specific cancers treated by each of these anticancer agents are well known to one skilled in the art. For example, Williams and Lemke, *Foye's Principals of Medicinal Chemistry.*,5th ed. Baltimore: Lippincott, Williams, & Wilkins, 2002, 928-945 (a copy of which is attached) indicate, which cancers these anticancer agent are currently used or approved for treating. Other sources, such as the Nation Cancer Institute, as well as the FDA indicate specific cancers that these anticancer agents can be used for treating.

Applicants have discovered that these anticancer agents (as well as other anticancer agents) can function at least in part by forming AP sites of DNA of the specific cancer cells the agents are administered to treat. Specifically, the present application states at page 17 that:

> "Injury to DNA is minimized by enzymes that recognize errors, remove them, and replace the damaged DNA with corrected nucleotides. DNA damage occurs when a single-strand break is introduced, a base is removed leaving its former partner unpaired, a base is covalently modified, a base is converted into another that is not appropriately paired with the partner base, or a covalent link is introduced between bases on opposite strands. Excision repair systems remove the mispaired or damaged base from the DNA strand and then synthesize new DNA to replace it. Base excision repair (BER) is initiated during replication of DNA and allows for correction of damaged bases/mispaired bases prior to completion of replication.
> Base excision repair is initiated by a DNA glycosylase that removes N-glycosidic (base-sugar) bonds, liberating the damaged base and generating an abasic site (AP site). An apurinic or apyrimidinic site results from the loss of a purine or pyrimidine residue, respectively, from DNA. uracil residues result from the spontaneous deamination of cytosine and can lead to a C-T transition if unrepaired. There is also a glycosylase that recognizes and excises hypoxanthine, the deamination product of adenine. Other glycosylases remove alkylated bases (such as 3-methyladenine, 3-methylguanine, and 7-methylguanine), ring-opened purines, oxidatively damaged bases, and in some organisms, UV photodimers.
> The AP site is further processed by a 5'-3' endonuclease (AP endonuclease (APE)) that incises the phosphodiester bond on both sides of the damaged purine or pyrimidine base. The AP endonucleases introduce chain breaks by cleaving the phosphodiester bonds at the AP sites."

The present application also teaches that the BER inhibitors can potentiate the effect of these cancer agents by inhibiting base excision repair, which is one of the mechanisms the cancer cells use to inhibit the cytoxic function of the anticancer agents.

Applicants have also provided working examples in the present application to show that BER inhibitors can be used to potentiate the effect of anticancer agents that form AP sites. Specifically, Example 1 of the present application shows that methoxyamine, a BER inhibitor, potentiates the effect of TMZ, an anticancer agent that induces formation of AP sites; Example 4 shows that BER inhibitors potentiate

the effect of chlorethylating agents that induce formation of AP sites; Example 10 shows that BER inhibitors potentiate the effect of an oxidizing agent that induces formation of AP sites in cancer cells; and Example 11 shows that BER inhibitors potentiate the effect of radiosensitizing agents.

Thus, the appropriate question for determining whether the enablement requirement has been satisfied in the present case is whether the instant specification teaches the ordinary skilled artisan a method of administering a BER inhibitor in combination with an anticancer agent that induces formation of AP sites for the treatment of cancer. Applicants respectfully submit that one skilled in the art would have been able to perform the foregoing methods based on the specification as well as the examples noted in the specification.

Moreover, the Office Action provides no evidence to doubt the veracity of the objective statements made in the specification. It is well established that "[t]he examiner has the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention" *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A requirement for some experiment does not prevent the satisfaction of the enablement requirement. *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1329 (Fed. Cir. 1990). The Federal Circuit has made it clear that "[w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, *providing sufficient reasons for doubting*

any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1561-1562 (Fed. Cir. 1993). (Emphasis added).

Specifically, the Examiner has not provided any factual evidence or reason to doubt the objective truth of Applicant's statements, which must be relied upon for enabling support; namely, that the claimed BER inhibitors can potentiate the effect of anticancer agents that induce the formation of AP sites. Instead, the Examiner cites one reference, Suggitt and Bibby, Clinical Cancer Research, 2005, Vol 11, 971-988 to show that in certain cases the treatment of cancer is unpredictable and that current tumor cell line in vitro screen is unpredictable. The fact that this reference teaches that treatment of cancer is unpredictable does not provide any basis to doubt the expectation of success of the current methods. The reference does not teach the administration of BER inhibitors in combination with anticancer agents that induce formation of AP sites. In fact, there is no mention of the mechanism involved in the present application. Difficulty in testing the compounds as cited in the reference has no bearing on the efficacy of the treatment method, particularly, since the application employs known cancer agents that have been approved for treating known cancers.

Accordingly, for the reasons of record and in contrast to the Examiner's assertions, the instant specification does enable one skilled in the art to practice the claimed invention and it would not require undue experimentation to practice the invention as claimed. Moreover, the reference relied upon by the Examiner provides no evidence that the claimed invention could not be successfully practiced.

Applicants, therefore, request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, rejection of claim 59.

Claims 60, 64, 65, 75, 77, 78, and 98 depend either directly or indirectly from claim 59, therefore, Applicants respectfully request that the 35 U.S.C. §112, first paragraph, rejection of claims 60, 64, 65, 75, 77, 78, and 98 also be withdrawn.

Claims 70 and 93 were cancelled. Therefore, rejection of these claims based on 35 U.S.C. §112 is moot.

3. 35 U.S.C. § 102 rejection of claims 59-60, 70, 75, and 98

Claims 59-60, 70, 75, and 98 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffin et al. (Biochemie (1995) 77, 408-422) (hereinafter, "Griffin et al.").

The Office Action argues that Griffin et al. teach that PARP inhibitors enhance temozolomide-induced DNA strand breaks and increase temozolomide induced toxicity where temozolomide is known to induce the formation of AP sites.
The Office Action notes that any treatment, people or cells, with both compounds is known to potentiate a therapeutic effect.

As discussed above, Claim 59 has been amended to recite that the BER inhibitor is selected from the group consisting of an AP endonuclease inhibitor, a DNA glycosylase inhibitor, a DNA polymerase inhibitor, and a DNA ligase inhibitor. Claim 59 is patentable over Griffin et al. because claim 59 limits the BER inhibitor to an AP endonuclease inhibitor, a DNA glycosylase inhibitor, a DNA polymerase inhibitor, and a DNA ligase inhibitor and does not recite that the BER inhibitor is a PARP inhibitor. Griffin et al. teaches the administration of a PARP inhibitor in

combination with temozolomide to increase temozolomide cytotoxicity. Claim 59 does not include the administration of PARP inhibitors and is not anticipated by Griffin et al. Therefore, withdrawal of the rejection of claim 59 is respectfully requested in view of the present amendment.

Claims 60, 75 and 98 depend directly or indirectly from claim 59 and therefore should be allowable because of the aforementioned deficiencies discussed above with respect to the rejection of claim 59 and because of the limitations recited in claims 60, 75 and 98.

Claim 70 and 99-100 have been cancelled and are no longer pending in the present application.

In view of the foregoing, it is respectfully submitted that the above-identified application is in condition for allowance, and allowance of the above-identified application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this amendment to our Deposit Account No. 20-0090.

Respectfully submitted,

/Richard A. Sutkus/
Richard A. Sutkus
Reg. No. 43,941

TAROLLI, SUNDHEIM, COVELL,
& TUMMINO L.L.P.
1300 East Ninth Street, Suite 1700
Cleveland, Ohio 44114
Phone: (216) 621-2234
Fax: (216) 621-4072
Customer No.: 68,705